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T CORTICAL-SUBCORTICAL RELATIONSHIPS OF THE CHIMPANZEE

DURING DIFFERENT PHASES OF SLEEP

(J.M. Rhodes, M. R. Reite, Dan Brown, ^{and} W. R. Adey)

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Brain Research Institute, University of California at Los Angeles,
Los Angeles, California.

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If accepted, please send proofs to:

Dr. J. M. Rhodes
Space Biology Laboratory, C3-384
Brain Research Institute
UCLA School of Medicine
University of California
Los Angeles, California 90024

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Although studies of differing states of consciousness, in particular those generally bearing the name of sleep, have been studied in many animals, the bulk of theoretical formulations have been based on two widely divergent species, cat and man.

Man's abiding interest in his own species, and the general availability of the cat for electrophysiology may well have led to this situation. However, subcortical recordings in man are still very much in the stage of clinical evaluation and usually performed in mentally deranged or the severely epileptic. Thus, most baseline information for man has come from scalp recordings. At the same time, although the cat has been extensively used for electrophysiological research few investigators would risk direct analogies between cat and man. The fact that they both sleep is hardly an adequate frame of reference, if we wish to understand how the human brain functions during sleep.

Our approach has been to take the opportunity to study one of the higher primates, the chimpanzee, with both cortical and subcortical recording leads. We hope to show certain relations between cortical and subcortical systems in differing sleep stages.

We have used stereotaxic procedures for the implantation of electrodes, with the aid of an atlas (in press) and stereotaxic apparatus prepared for the chimpanzee. A total of 18 to 27 leads were available in each of four animals, with 10 to 16 of these in subcortical structures. All recordings were bipolar. Subcortical recordings were made from bilateral hippocampal and amygdaloid placements, and from the rostral mid-brain reticular formation. Additional leads from the centrum medianum, entorhinal cortex, nucleus ventralis anterior and caudate nucleus were available in some subjects. Cortical recordings were made generally

from posterior skull screws, loosely termed occipital-parietal. Oculograms were also obtained and substantially supplemented by closed-circuit TV monitoring with a telephoto lens, which permitted a close view of the subject's face.

Our techniques of data analysis in the past 4 years have evolved from simple correlation analyses of the type instituted by Rosenblith and his colleagues at M.I.T. (M.I.T. Technical Report, 351 1959), to substantially more useful and complex techniques. We have initiated the use of cross-spectral and other forms of phase analysis techniques (Adey, Walter and Hendrix 1961; Adey and Walter 1963; Walter and Adey 1963; Walter 1963). The methods to be described here represent still further novel developments in EEG computer analysis. The computing devices have involved a variety of digital machines, principally an 8000 word, 12 bit core storage instrument of medium size, and a much larger 32,000 word, 36 bit computer. The latter is the only instrument capable of analyzing large amounts of data with the complex techniques to be described.

One of the first steps in our work has been to seek ways of defining basic sleep patterns in a way that might offer an acceptable scheme to the majority of investigators. In our opinion, the EEG of the chimpanzee more closely resembles that of man than that of lower animals when considered, for example in the broad categories such as can be seen in Fig. 1. Obviously, other more arbitrary categories could be established. However, greater refinement leads to other difficulties which we will discuss later. We have used the word "paradoxical" to describe that state of sleep with eye movements, relatively low voltage fast activity, etc. Our usage is based on personal experience in both man and the chimpanzee, where this state can seem behaviorally, to relate, to light or deep sleep and where

the EEG closely resembles an awake record. The apparent consistency of the paradoxical EEG in the cat may well relate to its simplified patterns in comparison with those from higher primates. It is possible, however, to see certain interesting relationships when using these admittedly broad categories of sleep - awake, spindling, slow wave and paradoxical. First, contrary to findings in the cat, the hippocampal leads tended to show very similar rhythms to those of the cortex in many phases of sleep, while the amygdala tended to retain its fast activity, except during the slow wave stage. Contrastingly, during the spindling phase a close relation can be seen between the fast spindle activity in the centrum medianum and the cortex (Fig. 1). These two types of activity can be seen more dramatically in Fig. 2 where the top panel shows the CM and cortical spindles while the bottom panel shows how the hippocampus and cortex may show a transient burst of shared high amplitude waves.

Fig. 3 demonstrates the possibility of setting up a number of additional categories in the range from drowsy states to moderately deep sleep. However, there is some difficulty in obtaining general agreement as to the exact sleep phase unless carefully taken in the context of the total EEG record. In trying to decide why there are such difficulties we closely examined some of the early stages. In Fig. 4 one may see the changes taking place during the first three dozing epochs and a light sleep. In the first drowsiness there is an increase in the rhythmicity of the cortical activity and the hippocampus begins to show high voltage slowing. In the second drowsiness the hippocampus shows less slow wave activity, but now the cortex shows higher voltage slowing. By contrast, in the third drowsy phase, the reverse is true. In the ensuing light sleep (or perhaps better called the "fourth drowsiness") there is a fragmentation of the cortical

rhythmicity accompanied by subcortical slowing with bursts of 14 - 16 cps activity in the hippocampus.

In an effort to define in another fashion these varying cortical-subcortical patterns, we used a series of click stimuli. Fig. 5 shows evoked responses to clicks, during different stages. During the awake stage, the spindle stage and the slow wave phase, the response is relatively constant in the rostral midbrain reticular formation, although decreasing progressively in the spindling and slow wave phases. However, in the drowsy stage, and in the two types of sleep with eye movements, there was great variability in the reticular response, with some increase in amplitude during the flattest of the paradoxical EEG states. This will be discussed further in average response computations. However, there is another phenomenon to be noted in Fig. 5. There are 2 stages of sleep with eye movements, one, which is labeled paradoxical and one labeled "amygdaloid spindle". The latter obviously resembles more closely the drowsy than an awake state. Yet, there is eye movement, although of a lower voltage than in the other paradoxical state.

This suggests to us that there are possibly several so-called paradoxical stages. Indeed, we feel that we have evidence of at least 2 other varieties but they remain incompletely categorized at this time. However, assuming more than one type of paradoxical sleep could certainly aid in understanding the conflicting reports as to depth of sleep during this stage and also possibly throw light on the relationships of dreams to these states. For example, one might consider levels of attention during dream activity. Moreover, we have seen muscle twitching and slight movements with amygdaloid spindles in contrast to the extremely large eye movements in the first paradoxical state. We are continuing our studies

of these states and hope to be able to define them more clearly with some new techniques which will be described later.

In further studies of evoked responses, we have recorded midbrain reticular responses, from an electrode probably placed very close to the lemniscus and, thus, giving the initial response, it is possible to see some dramatic changes during the different sleep stages, for example, the shifts in the secondary response in comparison to the awake state (Fig. 6). However, one of the more striking phenomena seemed to be the effect of the averaging as far as the signal-to-noise ratio was concerned. The signal during the drowsy and spindle stages tends to disappear in the averaging process in a similar fashion to that in the awake state, although in the drowsy state it is possible to discern an evoked response in the amygdala and hippocampus. During the slow wave stage one might expect to find the slow type of waves reflected in the averages. In the same way, it might be expected that in the amygdaloid spindle and paradoxical stages, the configuration of the averaged evoked response might be expected to resemble those in the awake-drowsy state. In fact, the slow evoked response was found here, but the amygdaloid spindle and paradoxical phases also showed increased slow components in evoked responses. This variability was quite striking and became more pronounced with changing the intensity of the clicks (Fig. 7). This produced a slight increase in response amplitude with increasing intensity during the waking state. A more obvious variability occurred during the paradoxical phase. We have also utilized a zero-crossing type of spectral analysis for on-line (immediate) computations. With this technique, the parieto-occipital cortex consistently showed slower frequencies during paradoxical sleep, but the amygdaloid rhythms were faster. This computed data has not been

extensively investigated as yet, but a more elaborate on-line spectral analysis will shortly be applied to this program.

This variability in the evoked responses was exemplified in the computed averages. The averaging for the paradoxical state has revealed much more rhythmicity than was seen in the wakeful animal. Yet, as is well known, without the appropriate cues it is difficult to state from the original EEG record which is paradoxical and which is awake. Furthermore, it is possible to see an enormous variability in the evoked response during paradoxical sleep, in both the amygdala and hippocampus.

So far we have tried to show (1) that the chimpanzee has an EEG similar to that of man, (2) that there is considerable variability during the initial stages of sleep with the cortex and subcortex showing varying electrical patterns until at least a medium (or spindle) stage of sleep is achieved, (3) that contrary to findings in the cat the hippocampal-neocortical rhythms are not inversely related, (4) that there may well be several stages of paradoxical sleep, with the rhinencephalon having a particularly important role.

The confusion which arises in categorizing differing states more completely, and the previously mentioned possibility of several states of paradoxical sleep led us to use a power spectral analysis. While this was interesting, and pointed up an EEG phenomenon usually overlooked in the high energy appearing at very low frequencies, no clear differences in dominant frequencies relating to differing sleep stages emerged from these spectral data, although the contours of the spectra varied in different states.

In an effort to quantify the distinctions which we saw in both the raw EEG data and the spectral analysis, we were led to stability measures. Stability in time is equivalent to the effective duration of a wave train.

Stability in frequency is the effective "spread" in frequency or bandwidth. Formulae for these parameters are shown in Fig. 8. The product of bandwidth and duration is known as the "uncertainty relation". We have defined the cross-plot of bandwidth versus duration as the stability diagram. Sinusoidal-like data characterized by long duration and narrow bandwidth move to the lower right. Spike-like data are characterized by the presence of many frequencies (wide bandwidth) and short duration moving toward the upper left hand corner. Various types of noise-like and modulated processes also have distinct signatures in the stability diagram.

When this technique was applied to EEG data collected on magnetic tape, the results were quite striking. Nine different segments from one night's run were chosen and classified as awake, drowsy, spindling, spindling-slow wave mixtures, slow wave, paradoxical, amygdaloid spindling, (or paradoxical II), and awakening (Fig. 9). The analyzed output of records from the parieto-occipital cortex, entorhinal cortex and midbrain reticular formation were then plotted on the diagram and the slower stages separated quite readily from the faster stages. Within the regions of faster activity there were rather consistent patterns and directionability going from awake to paradoxical to drowsy to waking with the stage of amygdaloid spindles tending to be between the faster activity and slower. However, a similar analysis (Fig. 10) of the same sleep stages for the amygdala and hippocampus showed striking differences. These relationships for the amygdala appeared to move in the opposite direction. This time, however, the amygdaloid spindling stage is located extremely close to the paradoxical. However, these analyses for the hippocampus (Fig. 10) are sharply contrasting, with both the awake and amygdaloid-spindle stages in

unexpected locations in relation to the slow and fast activity clusters. Since this is a new technique for examining EEG activity, it is emphasized that more familiarity with the analytic procedures will be necessary before making any rigorous interpretations. However, when one goes to the original autospectra, as in Fig. 11A, one interpretation is immediately suggested.

Although only 3 of the differing sleep stages have been plotted in Fig. 11, it is obvious that nearly all the power is in the low frequency range, and that the spectra separate only in the high frequency range, containing less than one percent of the power. Our present frequency analysis programs compute the spectrum by first performing an auto-correlation function and then taking the Fourier transform as an estimate of the spectrum. This method tends to distort low spectral values in the presence of narrow-band peaks. There are some indications of peaks in the spectra in the neighborhood of 6 cps. which is masked by the essentially "zero-frequency" data. In general, the spectral magnitudes above 10 cps are less than one percent of the magnitude at low frequency. These levels are at the dynamic range limit of the present technique; thus the position and magnitude of calculated peaks are thought to be unreliable. A new computer program has been written and is currently being tested that should avoid this ambiguity. It is possible to see that this low frequency power existed in all the leads, for example, the parieto-occipital cortex (Fig. 11B), somewhat smaller in magnitude in the reticular formation (Fig. 11C) but still obvious. The question thus arises as to how we find our stability measure when we are essentially looking only at very low frequency data. In fact, when the EEG records are read, this very slow data is generally ignored by the reader as it is irregular and difficult to see in comparison with the faster activity. Yet it can be used quite effectively for the

separation of differing states particularly those at the wakeful end of a sleep continuum. Thus, we feel that this technique may well afford a substantial increment in understanding of both slight changes in the state of consciousness and in those states of sleep called paradoxical.

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LEGENDS TO FIGURES

Fig. 1. Typical EEG record in four different states of sleep and wakefulness in the chimpanzee. Abbreviations: R. AMYG., right amygdala; L. HIPP., left hippocampus; R. HIPP., right hippocampus; R.C.M., right centrum medianum; RMDRF, right midbrain reticular formation; P-O. CX., parietal-occipital cortex; E. M., eye movements.

Fig. 2. Examples of regional functional interrelation in cortico-subcortical systems. Part A displays spindle activity simultaneously in the nucleus centrum medianum (RCM) and in the parieto-occipital cortex (P-O.CX). Part B shows a similar selective relationship between the hippocampus (R. HIPPO.) and P-O. CX. All abbreviations as in Fig. 1.

Fig. 3. Establishment of sleep categories on the basis of EEG records
(See text). Abbreviations as in Fig. 1.

Fig. 4. Changing patterns in both amplitude and rhythmicity during a sequence of drowsy episodes leading to light sleep. Abbreviations as in Fig. 1.

Fig. 5. A series of epochs of EEG records (A-F) during presentation of trains of 50 clicks presented at intervals of 4 seconds. In E, the designation AMYGDALOID SPINDLES refers to a different type of paradoxical sleep from that shown in Part D. All other abbreviations as in Fig. 1.

Fig. 6. Averages of 50 evoked responses to clicks prepared on a general purpose digital computer, and covering states from wakefulness to slow-wave and paradoxical sleep. Analysis time is 3.9 seconds, stimulus delay was 100 ms. Abbreviations: ENT. CX, entorhinal cortex; other abbreviations as in Fig. 1.

Fig. 7. Averages of 50 evoked responses prepared on a general purpose digital computer. Analysis time was 3.9 seconds and the stimulus delay was 100 ms. Averages were prepared at progressively increasing intensities of clicks (1 = 1 to 4). Abbreviations as in Fig. 1.

Fig. 8. Formulation of bandwidth-duration characteristics of a random function, as a function of its power spectrum, amplitude and variance.

Fig. 9. Bandwidth-duration for three different electrode placements (parietal-occipital cortex, entorhinal cortex, midbrain reticular formation) during nine different states from wakefulness to deep sleep. Symbols are: A, awake; D, drowsy; W, waking; SL, slow; SP, spindles; SS, slow waves and spindles mixed; P, paradoxical; AS, amygdaloid spindles (paradoxical II).

Fig. 10. Bandwidth-duration diagram for amygdaloid and hippocampal electrode placements during the nine different states shown in Fig. 9.

Fig. 11. Power spectra for the hippocampal lead (A), parietal-occipital (B), and the midbrain reticular formation (C) during three different behavioral states.